least groups I-V of the present invention. The single inventive concept is the use of alkanoic acids for the production of mature recombinant proteins in situ, as specified in claims 1 and 40.

The Group I invention recites the method for obtaining a mature protein in a cell culture supernatant using alkanoic acid.

The Application states that the protein precursors may be used for enzyme precursors (zymogens) or hormone precursors or proteases, as disclosed at page 4, lines 18-23. Please notethe specific examples of precursor proteins encoded by corresponding DNA or cDNA sequences that are identified at page 4, lines 18-23.

In a preferred embodiment the precursor protein is a pre-pro-enzyme and the most preferred pre-pro-enzyme is pre-prourokinase. This particular embodiment of the Group I invention, which is pointed out in new claim 42, uses alkanoic acids and a cDNA precursor encoding for pre-prourokinase. A further embodiment of Group I is recited in new claim 43 which points out the method for using alkanoic acids in production of the mature and catalytically active tc-uPA from the culture medium. This shows that the single inventive concept is present through the sequential steps leading to the production of an isolated mature protein.

The mature, catalytically active tc-uPA, either natural or recombinant, is a heterogeneous molecule consisting of High and a Low Molecular Weight forms (HMW and LMW respectively), as reported in the literature and in the present application at page 6, lines 4-10; page 4, line 32; and page 5, lines 1-2. Typically, once mature protein is obtained in the cell culture supernatant (Group I), further purification is performed to achieve a pharmaceutical grade compound. Generally, chromatographic methods are preferred over immunologic methods for purification of pharmaceutical grade compounds. Purification of mature tc-uPA which is particularly suited for pharmaceutical purposes, as described in the present application, provides for further separation of the two forms.

For these reasons, ion-exchange chromatography is performed on the cell supernatant to separate the HMW and LMW tc-uPA by a differential release under different ionic and pH conditions. Further purification is separately performed on HMW and LMW by affinity chromatography on a benzamidine column, according to known methods. These methods merely represent ssubsequent steps in a particular embodiment of the group I invention. Accordingly, the whole process for HMW and LMW purification, defined in group II and group III inventions, represents subsequent steps in particular embodiments of the Group I invention.

The product claims, corresponding to Group IV and Group V inventions represent the final product of each of Group I, Group II and Group III processes according to the specific embodiment of new claim 42.

It is believed that the foregoing remarks have demonstrated that there is a single inventive concept in the claims before the Examoiner. New claims 40 to 68 have been added to more precisely point out the common inventive step of Groups I-V. Claims 1, 40-42, 44-53 and 56 read on the elected invention of Group I. Claims 43, 54, 55 and 57-60 read on Groups II and III. Claim 61 reads on Group V. Claim 62 reads on Group IV. Claims 63-68 read on Groups VI and VII.

An early and favorable action is earnestly solicited.

Respectfully Submitted

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